## REMARKS/ARGUMENTS

Claims 33, 38-40 and 44-53 are pending in this application. Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, first and second paragraphs, and 35 U.S.C. §102(a).

The remaining objection and rejections of Claims 33, 38-40 and 44-53 under 35 U.S.C. §§101 and 112, first paragraph, are addressed below.

### Oath/Declaration

The Examiner maintains that the oath or declaration of the present application is defective because non-initialed and/or non-dated alteration have been made to the oath or declaration (for inventor Dan Eaton). More specifically, the Examiner alleges that "Applicant failed to note the conjunction of 'dated' and 'initialed' as one unit." The Examiner further contends, "The signature and date concerns the Oath/Declaration proper and not alterations which are covered by 37 C.F.R. §1.52(c)."

Applicants respectfully disagree.

Applicants respectfully submit that 37 C.F.R. §1.52(c)(1) states:

> (c)(1) Any interlineations, erasure, cancellation or other alteration of the application papers filed must be made before the signing of any accompanying oath or declaration pursuant to §1.63 referring to those application papers and should be dated *and* initialed or signed by the applicant on the same sheet of paper. (Emphasis added).

Applicants respectfully submit that the Examiner has misinterpreted 37 C.F.R. §1.52(c) to simply require "dated and initialed" as "one unit" requirement. Rather, Applicants submit that 37 C.F.R. §1.52(c)(1) has three requirements for an applicant making an alteration in the oath or declaration. First, the oath or declaration must be dated. Second, the oath or declaration must be initialed or signed. Finally, the date *and* initial or signature of the Applicant must be on the same sheet of paper.

Applicants note that inventor Dan Eaton initialed below the address change and dated the declaration on the same page. Although Dr. Eaton did not date the declaration next to his initial,

Applicants submit that 37 C.F.R. §1.52(c)(1) does not require that the date be next to the initial. In fact, 37 C.F.R. §1.52(c)(1) only requires that the initial or the signature of the applicant be on the same page as the date and not necessarily be adjacent to each other.

Nevertheless, without acquiescing to the Examiner's position in the current objection, solely in the interest of expediting prosecution in this case, Applicants respectfully submit a new declaration which includes a substitute page reflecting the correct address for Dr. Dan Eaton that is dated and signed by Dr. Dan Eaton.

Applicants note that signatures of remaining inventors are as originally submitted in the present application and the new declaration was not executed by the remaining inventors.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objection.

## Priority Determination

Applicants thank the Examiner for granting the priority of the instant application as June 23, 1999.

## Claim Objections

Claim 48 is objected to allegedly because of "typos 'of an at', 'use'." The Examiner further objects Claim 48 allegedly because the use of "a complement" makes it unclear which complement is claimed.

Applicants respectfully submit that Claim 48 recites, "An isolated nucleic acid molecule consisting of an at least 50 nucleotides fragment of the nucleic acid sequence of SEQ ID NO:276, or a complement thereof, that specifically hybridizes under stringent conditions to ...."

Accordingly, Applicants fail to note a typographical error in the claim.

Applicants further submit that Applicants are simply claiming a fragment of the nucleic acid sequence that is at least 50 nucleotides long which is from either SEQ ID NO:276 or a complement of SEQ ID NO:276. Accordingly Applicants believe that the use of the term "a complement" is clear and no amendment to the claim is required.

Consequently, Applicants respectfully request the Examiner to reconsider and withdraw the objection.

**Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph**

Claims 33, 38-40 and 44-53 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 33, 38-40 and 44-53 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art would not know how to use the claimed invention."

For the reasons outlined below, Applicants respectfully disagree and traverse the rejections.

**Utility – Legal Standard**

According to 35 U.S.C. §101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added).

In interpreting the utility requirement, in *Brenner v. Manson*[1], the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, *i.e.,* a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler,*[4] the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka,*[6] the CAFC reaffirmed *Nelson* and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The Court perceived "no insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the

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[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines"),[15] which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public"

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[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility'."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

**Proper Application of the Legal Standard**

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the nucleic acid sequence encoding the PRO1317 polypeptide for the reasons previously set forth in the Applicants' response filed on December 20, 2004 and below.

The Examiner alleges that "SEQ ID NO:276 is elevated in a relative, non-quantitative assay of genes from a lung tumor sample." Furthermore, the Examiner alleges, "Overexpression of a single gene is not necessary or sufficient to indicate whether the tumor is malignant or benign, establish vascularization, or its potential for metastasis." Finally, the examiner contends, "the commercially available tumor tissues used in the Specification lack any detailed information about the tumors used."

Applicants respectfully disagree and traverse the rejection.

First of all, Applicants respectfully submit that the gene amplification assay is well-described in Example 143 of the present application. As previously discussed in the Applicants' response of December 20, 2004, the nucleic acids encoding PRO1317 had $\Delta$Ct value of > 1.0, which is **more than 2-fold increase**, for primary lung tumors LT1, LT1a, LT9, LT10, LT15,

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[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II(B)(1).

LT17 and LT22. Therefore, PRO1317 showed approximately 1.15 to 2.69 ΔCt unit which corresponds to $2^{1.15}$ to $2^{2.69}$ - fold amplification or 2.219 to 6.453 fold amplification in primary lung tumors. Therefore, Applicants have clearly shown that the nucleic acid sequence of SEQ ID NO:276 is amplified in a well-established and quantitative assay.

Secondly, regarding the Examiner's assertion that "overexpression of a single gene is not necessary or sufficient to indicate whether the tumor is malignant or benign, establish vascularization, or its potential for metastasis", Applicants respectfully submit that the Examiner has not established a *prima facie* case for lack of utility for the nucleic acid sequence of SEQ ID NO:276.

MPEP §2107.02(IV) states, "To properly reject a claimed invention under 35 U.S.C. 101, the Office must: (A) make a *prima facie* showing that the claimed invention lacks utility, and (B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. *In re Gaubert*, 524 F.2d 1222, 1224, 187 USPQ 664, 666 (C.C.P.A. 1975)." Applicants note that the Examiner has not provided any evidentiary basis for Examiner's assertion indicating why overexpression of a single gene, SEQ ID NO:276 is not sufficient to indicate that SEQ ID NO:276 would be useful as a diagnostic marker of human lung cancer.

Further, Applicants respectfully submit, "There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed." *Ex parte Feguson*, 117 USPQ 229 (Bd. App. 1957); *see also* M.P.E.P. §2107.02(VII). Furthermore, M.P.E.P. §2107.02(VII) states that

> the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-34 (CCPA 1980).

Accordingly, Applicants respectfully submit that when the proper evidentiary standard is applied, overexpression of a single gene SEQ ID NO:276 based on the disclosure in the present specification, is sufficient to establish an asserted utility for the nucleic acid sequence of SEQ ID

NO:276, for example, as a marker for the diagnosis of cancer.

In addition, contrary to the Examiner's assertion that the specification lacks any detailed information about the tumors used, Applicants respectfully submit that the specification clearly provides detailed information about the tumors used in the gene amplification assay. For example, each lung cancer and cancer cell line in the gene amplification assay represents different types, stages and physiological conditions of a lung tumor. For example, on page 331, line 37 of the specification states, "The primary lung cancers were obtained from individuals with tumors of the type and stage as indicated in Table 8." Further, on page 337, line 9, the specification discloses that Table 8 describes "T stage and N stage of various primary tumors which were used to screen the PRO polypeptide compounds of the invention."

Applicants respectfully submit that lung cancer staging is the process of finding out how localized or widespread the cancer is. Each stage describes how far the cancer has spread. A treatment and prognosis depend on the cancer's stage.

The system used to describe the growth and spread of non-small cell lung cancer (NSCLC) in the instant application is the TNM staging system. T stands for tumor (its size and how far it has spread within the lung and to nearby organs), N stands for spread to lymph nodes, and M is for metastasis (spread to distant organs). In TNM staging, information about the tumor, lymph nodes, and metastasis is combined and a stage is assigned to specific TNM groupings. The grouped stages are described using the number 0 and Roman numerals from I to IV (1 to 4).

Accordingly, Table 7 also shows that these tested lung tumors and tumor cell lines are from various growth stages, such as IA, IIA, IIIA, IB, IIB, etc., or T1, T2, or T3, or N0, N1, or N2 stages.

Hence, Applicants submit that specification provides clear and detailed information about the tumors used in the gene amplification assay.

The Examiner alleges that Applicants' assertion of utility is "not specific because Applicant has not made a positive assertion of the polynucleotide of SEQ ID NO:276's or the polypeptide of SEQ ID NO:277's identity." The Examiner contends that Applicants did not positively identify the polynucleotide of SEQ ID NO:276 as tumor suppressor gene or proto-

oncogene.

The Examiner is applying an inappropriate test. The law clearly states that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works. "*Newman v. Quigg*, 11 USPQ2d 1340 (Fed. Cir. 1989). Accordingly, the disclosure or identification of such a mechanism is not required in order to establish the patentable utility of the polynucleotide of SEQ ID NO:276.

Applicants respectfully submit that the present application discloses at least one credible, specific and substantial asserted utility for the nucleic acid sequence SEQ ID NO:276 encoding the PRO1317 polypeptide. The gene amplification data clearly shows that SEQ ID NO:276 was amplified in a number of primary lung tumors and thus would be useful as a diagnostic marker of human lung cancer.

The Examiner also alleges that Applicants assertion is not substantial because "it would constitute additional experimentation to first determine the identity of polynucleotide of SEQ ID NO:276, then to determine the use the nucleic acid of SEQ ID NO:276." Therefore, Examiner concludes that the asserted utility for the claimed nucleotide of SEQ ID NO:276 is not substantial "since significant further research would be required of the skilled artisan to determine what its properties are."

As discussed above, the law does not require Applicants to correctly set forth, or even know, how or why the invention works to establish the patentable utility. Accordingly, it is not necessary for Applicants to identify the biological properties or mechanism for the claimed biological function. The instant specification clearly discloses that the polynucleotide of SEQ ID NO:276 is amplified in a number of lung tumors.

Further, Applicants respectfully submit that the amplification of the nucleic acids in even one lung tumor provides specific and substantial utility for the nucleic acid as a diagnostic marker of the type of lung tumor in which it was amplified. Applicants submit that the tumors listed in Table 8 are not similar tumors from different patients, but various types/classes of lung and/or colon tumors at different stages. Accordingly, a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used

as a marker for diagnosing the presence of that kind of tumor in which it was amplified. Amplification of the nucleic acid would be indicative of that specific class of lung tumor, whereas absence of amplification would be non-conclusive.

Therefore, no further research is required to establish the patentable utility of the plynucleotide of SEQ ID NO:276. Accordingly, Applicants have demonstrated a credible, specific and substantial asserted utility for the polynucleotide of SEQ ID NO:276, for example as a marker for the diagnosis of cancer.

The Examiner contends that Declarations under 37 C.F.R. §1.132 by Dr. Goddard is insufficient to overcome the rejection of Claims 33, 38-40 and 44-53 based upon lack of utility and lack of enablement. The Examiner further alleges

> The PRO1317 gene (nucleic acid of SEQ ID NO:276 and amino acid of SEQ ID NO:277) has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the nucleic acid of SEQ ID NO:276 was amplified in some lung tumor tissues, to a minor degree (about 2.5 fold). No mutation or translocation of PRO1317 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1317 is expressed in corresponding normal tissues or what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the polynucleotide encoding PRO1317 is amplified in a variety of samples, including some normal tissues, and invite the artisan to determine the significance of this increase.

Applicants respectfully disagree and traverse the rejection.

As mentioned above and in the Applicants' response of December 20, 2004, the nucleic acids encoding PRO1317 had $\Delta$Ct value of > 1.0, which is **more than 2-fold increase**, for primary lung tumors LT1, LT1a, LT9, LT10, LT15, LT17 and LT22. Therefore, PRO1317 showed approximately 1.15 to 2.69 $\Delta$Ct unit which corresponds to $2^{1.15}$ to $2^{2.69}$ - fold amplification or 2.219 to 6.453 fold amplification in primary lung tumors. Accordingly, Applicants have clearly shown that the PRO1317 gene is associated with tumor formation or the development of cancer.

Therefore, contrary to the Examiner's assertion on page 9 of the Office Action that "the

specification provides data showing a very small increase in DNA copy number- about 2.3 fold- in a two different types of tumors," Applicants submit that the PRO1317 nucleic acid was amplified in a significant number of lung tumors and showed 2.219 to 6.453 fold amplification in these tumors. In addition, the previously submitted Declaration by Dr. Audrey Goddard clearly states:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Therefore, any gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay is considered useful as a marker for the diagnosis of cancer.

The Examiner further alleges, "One cannot determine from the data in the specification whether the observed 'amplification' of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates." (See page 7 of the instant Office Action). The Examiner further cites Sen to content that "chromosome aberrations known as aneuploidy are commonly observed in tumors." (See page 10 of the instant Office Action).

In response, Applicants refer to the previously submitted Declaration by Dr. Avi Ashkenazi, Ph.D. In particular, Dr. Ashkenazi is in opinion that gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker. As a result, the present gene amplification assay is a well-controlled experiment and give rise to data of biological significance. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long

as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

The Examiner contends that Pennica *et al.* shows that "the issue is simply not predictable, and the specification presents a mere invitation to experiment." Applicants respectfully submit that Pennica *et al.* discloses a correlation between DNA amplification and over-expression of mRNA levels. Pennica *et al.* do not address the issue relating to gene amplification of nucleic acid due to increase in chromosomal copy number or aneuploidy. Therefore, Applicants fail to see the relevance of Pennica *et al.* regarding this issue.

The Examiner also contends that "the [Goddard] Declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Goddard's conclusions are provided in the declaration."

Applicants have submitted Dr. Goddard's Declaration to show that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1317 is a diagnostic marker of lung cancer. Applicants emphasize that the opinions expressed in the Goddard Declaration are all based on factual findings. Thus, Dr. Goddard explains that the TaqMan PCR assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. Further, Dr. Goddard explains that the assay is extremely sensitive technique which leads to accurate determination of gene copy number. Dr. Goddard adds that the TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. For support, Dr. Goddard cites a number of references including a publication by Pennica *et al.* in which Dr. Goddard is a co-author of the paper. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for

monitoring cancer development and/or for measuring the efficacy of cancer therapy. Thus, Dr. Goddard's statement that "a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Goddard would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[18] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument."[19] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner."[20] Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[21] which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement from an expert in the field (the Goddard Declaration) states that "it is my considered scientific opinion that ... a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer." Therefore, barring evidence to the contrary regarding the above statement

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[18] *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (CCPA 1976); *In re Piasecki* 745 F 2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[19] *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[20] *In re Alton, supra.*

[21] Part IIB, 66 Fed. Reg. 1098 (2001).

in the Goddard Declaration, this rejection is improper under both the case law and the Utility guidelines.

The Examiner cites Hu *et al.* for support that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease.

First of all, Applicants respectfully submit that the present application is directed to the nucleic acid sequence of SEQ ID NO:276 which encodes the PRO1317 polypeptide. Therefore, Applicants fail to see the relevance of the Examiner's rejections for lack of utility in the instant Office Action that are directed to the alleged lack of utility for the PRO1317 polypeptide.

Nevertheless, Applicants respectfully submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Accordingly, contrary to the Examiner's assertion, Applicants respectfully submit that Hu *et al.* does not conclusively show that it is more likely than not that the gene amplification does not result in increased expression at the mRNA and polypeptide levels.

First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based a statistical analysis of the information disclosed in published literature. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants submit that the reference by Hu *et al.* only studies the statistical analysis of micro-array data and not the gene amplification data. Hence, their findings would not

be directly applicable to the gene amplification data. In addition, the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes.

Further, the analysis by Hu *et al.* has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (Emphasis added). Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules were overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusion based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the

conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al.* admit that "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

Accordingly, Applicants respectfully submit that the Examiner has not shown that a lack of correlation between microarray data and the biological significance of cancer genes.

The Examiner alleges that "there is no evidence whether or not PRO1317 mRNA or polypeptide levels are also increased in this cancer." The Examiner cites the Haynes *et al.* reference to establish that "protein levels cannot be accurately predicted from the level of corresponding mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold."

As mentioned above, Applicants respectfully submit that present application is directed to the PRO1317 nucleic acids and not the PRO1317 polypeptides. Therefore, Applicants fail to see the relevance of the Examiner's rejections for lack of utility in the remainder of the instant Office Action that are directed to the alleged lack of utility for the PRO1317 polypeptide and its antibodies. (See pages 9-13 of the instant Office Action).

The Examiner asserts, "The instant disclosure is silent as to the actual biological activity or function of the polynucleotide of SEQ ID NO:276." The Examiner further alleges that "[b]ecause the instant specification does not provide some minimal context as to what altered levels of the polynucleotide of SEQ ID NO:276 mean the artisan can find no therapeutic utility for the claimed antibodies because significant and substantial further research would need to be performed in order to answer these simple but vital questions." Therefore, the Examiner

concludes, "it is not clear how the skilled artisan would use the claimed nucleic acids for therapeutic uses."

Applicants respectfully disagree and traverse the rejection.

As discussed above, Applicants respectfully submit that the gene amplification data shown in the present application clearly demonstrates that the nucleic acid of SEQ ID NO:276 is amplified in at least 7 primary lung tumors. Thus, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polynucleotides, for example, as a marker for the diagnosis of cancer.

Accordingly, based on this information one skilled in the art at the effective priority date of this application would have accepted that the nucleic acid encoding PRO1317 meets the utility requirement of the 35 U.S.C. §101 as a diagnostic marker for cancer. Further, based on this utility and the disclosure in the specification, one skilled in the art would know how to use the claimed antibodies at the time of filing.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

**Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)**

Claims 48-53 are rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. In particular, the Examiner alleges that "the specification fails to provide any guidance for the successful production, isolation, and characterization of isolated nucleic acid comprising the SEQ ID NO:276 polynucleotide sequence or any variants, derivatives and fragments thereof."

For the reasons discussed below, Applicants respectfully submit that Claims 48-53 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph.

*The Legal Test for Enablement*

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art

at the time the invention was made, without undue experimentation.[22, 23] Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[24] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[25, 26]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re Wands* factors). The most important factors that must be considered in this case include: 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important."[27, 28] "Limitations and examples in the specification do not generally limit what is covered by the claims" M.P.E.P. § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as

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[22] M.P.E.P. §2164.01.

[23] *United States v. Telectronics, Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

[24] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (C.C.P.A. 1976).

[25] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (C.C.P.A. 1977).

[26] M.P.E.P. §2164.06.

[27] M.P.E..P. §2164.08.

[28] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (C.C.P.A. 1971).

broadly as it is claimed.[29]

*The specification provides sufficient information to enable the claimed invention*

First, Applicants respectfully maintain the position that that Claims 48-53 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' response filed on December 20, 2004.

Second, the specification clearly provides the sequence and methods for making PRO1317 starting on page 334 of the specification. More specifically, the specification describes methods for preparing PRO molecules starting on page 358. Further, Example 56 describes how to isolate the cDNA clones encoding PRO1317. Therefore, based on the disclosure in the specification, one skilled in the art would clearly know how to make and isolate the full-length PRO1317 nucleic acid sequence of SEQ ID NO:276. Therefore, the specification clearly provide guidance for the successful production, isolation, and characterization of isolated nucleic acid comprising the SEQ ID NO:276 polynucleotide sequence. Accordingly, the isolated nucleic acid sequence of SEQ ID NO:276 meets the enablement requirement under 35 U.S.C. §112, first paragraph.

Applicants respectfully submit that Claims 48 (and, as a consequence, those claims dependent from the same) does not claim any variants of SEQ ID NO:276, but only claims a fragment of SEQ ID NO:276, or complement thereof. Accordingly, Applicants respectfully submit that since the specification is enabling for the full-length nucleic acid of SEQ ID NO:276, the specification is also enabling for fragments of such that are usable as hybridization probes.

Applicants further submit that Claim 48 includes the specific stringent conditions used for hybridization. The nucleic acids claimed in Claim 48 and in dependent Claims 49-53 can be produced by recombinant and/or synthetic methods that were well known in the art at the priority date of the present application. In addition, one skilled in the art at the priority date of this

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[29] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir. 1999) (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

application would have been able to use such nucleic acids as PCR primers or probes, without undue experimentation, for example, in diagnostic assays based on the detection of the nucleic acid of SEQ ID NO:276 in lung tumors.

The Examiner has further indicated that variants, derivatives and fragments of SEQ ID NO:276 are not enabled due to various complications in predicting protein structure and function purely based on protein sequence prediction. (See pages 17-19 of the instant Office Action). In response, Applicants respectfully submit that the present application is directed to the PRO1317 nucleic acid sequences and not the PRO1317 polypeptides. Accordingly, Applicants fail to see the relevance of the Examiner's rejections.

Hence, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

**Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)**

Claims 48-53 remain rejected under 35 U.S.C. §112, first paragraph, allegedly as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleges, "The specification does not contain a written description of various derivative, fragments, complements, or hybridizable fragments of the claimed polynucleotide." Therefore, the Examiner concludes, "only isolated polypeptides [sic] comprising the nucleic acid sequence set forth in SEQ ID NO:276, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph." (See page 20 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection. For the reasons discussed below, Applicants respectfully submit that Claims 48-53 satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

*The Legal Test for Written Description*

The well-established test for sufficiency of support under the written description

requirement of 35 U.S.C. §112, first paragraph, is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[30, 31] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[32] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[33, 34]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[35] the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[36] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[37, 38].

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[30] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[31] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[32] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[33] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[34] *See also* M.P.E..P. §2163 II(A).

[35] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[36] *See also* M.P.E.P. §2141.03.

[37] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

*The specification provides sufficient written description for the claimed invention*

First, Applicants respectfully maintain the position that that Claims 48-53 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' response filed on December 20, 2004.

Second, Claim 48 recites, "An isolated nucleic acid molecule consisting of an at least 50 nucleotides fragment of the nucleic acid sequence of SEQ ID NO:276, or a complement thereof, that specifically hybridizes under stringent conditions to ...." Therefore, Claims 48 does not seek coverage of any nucleic acids that could be obtained under the specified stringent conditions, but claims a fragment of SEQ ID NO:276, or complement thereof. Further, as stated above, the Examiner has acknowledged that the nucleic acid sequence of SEQ ID NO:276 meets the written description provision of 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully submit that Claims 48-53 satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the present rejections under 35 U.S.C. §112, first paragraph.

**Claim Rejections – 35 U.S.C. §102**

Claims 48-53 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bonaldo *et al.* (*Genome Res.*, 6(9): 791-806 (1996)). The Examiner alleges that Bonaldo *et al.* disclose a nucleic acid which shares 100% homology with "SEQ ID NO: 282" for 150 base pairs.

First of all, Applicants respectfully submit that the present application is directed to the nucleic acid sequence of SEQ ID NO:276 and not SEQ ID NO:282. Secondly, since the Examiner did not provide the Accession Number for the cited sequence and no sequence alignment was included in the instant Office Action, Applicants are unable to determine which sequence disclosed in the Bonaldo reference has the 100% sequence homology with the 150 base pairs.

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[38] *See also* M.P.E.P. §2141.03.

Applicants would like to thank Supervisory Patent Examiner Brenda Brumback for telephone interview with Anna Barry on May 26, 3005 regarding the Bonaldo reference. Applicants submit that during the telephone conference with Ms. Brumback, Applicants and Ms. Brumback were unable to identify the cited sequence by Examiner Nichols in the Bonaldo reference.

Accordingly, Applicants respectfully submit that Claims 48-53 are not anticipated by Bonaldo *et al.* Hence, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Should the Examiner maintain the present rejection based on the Bonaldo reference, Applicants respectfully request an Accession Number for the cited sequence.

Claims 48-53 are further rejected under 35 U.S.C. § 102(e) as being anticipated by Sharp *et al.* (U.S. Patent No. 6,764,677), with the filing date of May 24, 2000. The Examiner alleges that SEQ ID NO: 18 of Sharp *et al.* discloses a nucleic acid which shares 100% homology with "SEQ ID NO: 282" for 2283 base pairs.

As mentioned above, Applicants respectfully submit that the present application is directed to the nucleic acid sequence of SEQ ID NO:276 and not SEQ ID NO:282. Applicants submit that SEQ ID NO:18 disclosed in Sharp *et al.* has only 47.29% sequence identity with SEQ ID NO:276 of the instant application. For support, Applicants enclose herewith a copy of the sequence alignment between SEQ ID NO:282 and SEQ ID NO:18 from U.S. Patent No. 6,764,677. In addition, SEQ ID NO:18 of the Sharp patent does not discloses a 50 contiguous nucleotide sequence having 100% sequence identity with SEQ ID NO:276 of the present application. Accordingly, Applicants respectfully submit that Claims 48-53 are not anticipated by Sharp *et al.*

Hence, the Examiner is respectfully requested to reconsider and withdraw the rejection under 35 U.S.C. §102(e).

## CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C59**).

Respectfully submitted

Date: May 27, 2005

By: 
Anna L. Barry (Reg. No. 51,436)

**HELLER EHRMAN LLP**
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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